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APPLICATION NUMBER:
202513Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 202513
Supporting document/s: 0000
Applicant's letter date: 8 February 2011
CDER stamp date: 8 February 2011
Product: Oxybutynin gel 3%
Indication: Overactive bladder
Applicant: Antares Pharma, Inc.
Review Division: Division of Reproductive and Urologic Products
Reviewer: Laurie McLeod-Flynn
Supervisor/Team Leader: Lynnda Reid
Division Director: Scott Monroe
Project Manager: Nenita Crisostomo

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1 Executive Summary

1.1 Introduction

Oxybutynin is a well characterized muscarinic antagonist, approved in oral and dermal forms for OAB. The pharmacokinetics and metabolism of oxybutynin are known in humans following both oral and transdermal administration, as is the safety profile of the drug.

1.2 Brief Discussion of Nonclinical Findings

No pivotal nonclinical studies were submitted with this NDA. All necessary studies were submitted for the Reference Listed Drug, Ditropan (5 mg). Oxybutynin 3% gel has been shown to result in clinical exposures to oxybutynin that are comparable to those of Ditropan.

Desethyloxybutynin, the pharmacologically active metabolite of oxybutynin, has a lower exposure level for oxybutynin 3 % gel than for Ditropan.

Cyclohexylmandelic acid or CHMA, the inactive metabolite of oxybutynin, is present as an impurity in oxybutynin 3% gel, and will have a specification limit set at (b) (4)

1.3 Recommendations

1.3.1 Approvability

There is no impediment to approval of this application from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

NA

1.3.3 Labeling

(b) (4)

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy

Category B. Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN administered to women who are or who may become pregnant has not been established. Therefore, DITROPAN should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN is administered to a nursing woman.

Pediatric Use

The safety and efficacy of DITROPAN administration have been demonstrated for pediatric patients 5 years of age and older.

2 Drug Information

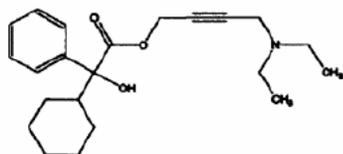
2.1 Drug

CAS Registry Number: 5633-20-5

Chemical Name: 4-(Diethylamino)-2-butynyl- α -phenylcyclohexaneglycolate

Molecular Formula/Molecular Weight: C₂₂H₃₁NO₃ / 357^{(b) (4)}

Structure or Biochemical Description:



Pharmacologic Class: muscarinic receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 70,527, NDA 17-577

2.3 Drug Formulation : Oxybutynin (3 %), diethylene glycol monoethyl ether, NF (DGME) (b) (4) (b) (4) (b) (4) hydroxypropyl cellulose, NF (b) (4) propylene glycol, USP (b) (4) butylated hydroxytoluene, NF (b) (4) HCl 0.1 (b) (4) (b) (4) (b) (4) purified water

2.4 Comments on Novel Excipients : NA

2.5 Comments on Impurities/Degradants of Concern

Phenylcyclohexylglycolic acid, cyclohexylmandelic acid or CHMA has been studied as an inactive metabolite of oxybutynin; it reaches concentrations approximately equal to unmetabolized oxybutynin after oral administration, and a (b) (4) limit for this impurity in the drug product has been previously exceeded in other oxybutynin based drug products. No toxicity of CHMA was predicted by FDA structure activity analysis.

2.6 Proposed Clinical Population and Dosing Regimen: Oxybutynin 3% gel will be indicated for adults with overactive bladder, with symptoms of urge urinary incontinence, urgency, and frequency. The recommended starting dosage is (b) (4) three pumps of ANTUROL (b) (4) 84 mg/day) applied once daily to clean, dry, intact skin on the abdomen, or upper arms/shoulders, or thighs. (b) (4)

(b) (4) Application sites may be rotated to reduce the potential for local site reactions.

2.7 Regulatory Background

This submission is a 505 (b)(2) application with Ditropan (5 mg) as the Reference Listed Drug. Oxybutynin has been in clinical use for OAB for over 30 years.

3 Studies Submitted

3.1 Studies submitted and reviewed

Drug Permeation Study in Pig Ear Skin with Oxybutynin Gel 3%

Cytotoxicity Study for Protocol No. 686647. (Extractables from container components)

4 Pharmacology

Oxybutynin chloride is a muscarinic receptor antagonist that inhibits bladder smooth muscle contraction. Its activity has been well characterized clinically, as described in the Ditropan label. It displays modest selectivity for M3 and M1 receptors over other subtypes (Yarker, 1995). Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. Following oral administration, oxybutynin is metabolized in the liver to the predominant active metabolite N-desethyloxybutynin (DEO) and to phenylcyclohexylglycolic acid (PCGA), a pharmacologically inactive metabolite. After oral administration, DEO is present in plasma at concentrations approximately 4-10 times higher than the plasma concentrations of the parent compound, oxybutynin. DEO has anticholinergic effects similar to oxybutynin. However, DEO has been suggested to be primarily responsible for the anticholinergic side effects (mainly dry mouth). By using controlled-release oral formulations, DEO plasma concentrations seen are 3-fold higher than that of oxybutynin. With transdermal administration, average plasma concentrations of DEO are 1-1.5 times higher than that of the parent compound (Zobrist, 2003).

Yarker Y et al. Oxybutynin: A review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging*. 1995; 6(3): 243-262.
Zobrist RH, Quan D, Thomas HM, Stanworth S, Sanders SW. Pharmacokinetics and metabolism of transdermal oxybutynin: in vitro and in vivo performance of a novel delivery system. *Pharm Res* 2003; 20(1):103-109.

5 Pharmacokinetics/ADME/Toxicokinetics

Oxybutynin is metabolized primarily, by CYP3A4, to phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active (activity similar to that of R-oxybutynin in *in vitro* studies.)

The clinical pharmacokinetics of Ditropan following administration of a 5 mg tablet are described in the Ditropan label.

Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following Three Doses of DITROPAN 5 mg Administered every 8 Hours (n=23)

Parameters (units)	R-Oxybutynin	S-Oxybutynin
C _{max} (ng/mL)	3.6 (2.2)	7.8 (4.1)
T _{max} (h)	0.89 (0.34)	0.65 (0.32)
AUC _t (ng·h/mL)	22.6 (11.3)	35.0 (17.3)
AUC _{inf} (ng·h/mL)	24.3 (12.3)	37.3 (18.7)

The rate and extent of skin permeation of oxybutynin delivered in the Anturol vehicle system used in the initial clinical studies were studied in vitro. The two permeation studies included one that provided a comparison of skin permeation in pig and human skin between a marketed transdermal product (Oxytrol TDS) and the formulation for which the Sponsor is seeking approval. The results of these studies demonstrated that the permeation rate of oxybutynin was 14.1 µg/cm² from the 3% gel and 75.6 µg/cm² from the Oxytrol patch. The amount of oxybutynin applied to the skin was 5.7 fold higher for the Oxytrol™ patch (1.7 mg vs. 0.3 mg in the 3% gel), indicating that the differences in permeation rates observed between the gel and the patch correlate well with the drug loading in the experiment. In a third study, the effect of a formulation change ^{(b) (4)} from the oxybutynin formulation for which the Sponsor is seeking approval was determined not to affect the permeation rate of oxybutynin from the new formulation ^{(b) (4)}. These findings supported the use of the same concentration of oxybutynin in the new formulation in a pharmacokinetic study to provide a clinical bridge between the new and old formulations.

Indirect comparison of C_{max} of R- and S-oxybutynin and R- and S-desethyloxybutynin for Anturol™ vs. Ditropan IR tablet (Referenced Listed Drug).

				Cmax OXY [ng/mL]			Cmax DEO [ng/mL]		
Product	Ref	N	Dosing	R-OXY	S-OXY	R/S OXY	R-DEO	S-DEO	R/S DEO
DITROPAN IR Tablet 5mg	[1]	18	Single dose (1 tablet once)	2.2	4.1	0.5	15.5	10.9	1.4
DITROPAN IR Tablet 5mg	[2]	23	5mg/8h (3 tablets over 24 hours)	3.6	7.8	0.5	n/a*	n/a	n/a
ANTUROL Gel 84mg	[3]	10	Day 7 (2.8g gel daily)	9.7**		n/a	8.9**		n/a

* n/a = not available **Individual R and S values not available.

[1] Zobrist RH et al. Pharm Res 2001;18(7):1029-1034

[2] Ditropan 5 mg Tablet Package Insert

[3] Antares Pharma Inc., unpublished data

Comparison of oxybutynin levels in oxybutynin 3% gel and other products

Product	Dosing	Cmax (ng/ml)	AUC (ng.hr/ml)
3% Gel	84 mg	9.7	156
Gelnique	100 mg	6.8 - 8.3	113 - 134
Oxytrol	3.9 mg/day	6.6	408
Ditropan*	5 mg IR	11.4	61.6

* Reference Listed Drug (RLD for oxybutynin 3% gel)

10 Special Toxicology Studies

Drug Permeation Study in Pig Ear Skin with Oxybutynin Gel 3%.

A study was performed in vitro comparing oxybutynin gel 3% with the Oxytrol™ patch. Two comparisons were performed: one with the same drug loading for gel and patch (54 mg of gel and 1.77 cm² of patch, both containing 1.6 mg of oxybutynin) and the other with a 10 mg gel dose, comparable to in vivo application conditions.

Each formulation was tested in 4 replicates (3 different donors). The thickness of each skin sample was measured with a micrometer. The samples were mounted on vertical glass Franz diffusion cells with a receptor compartment of 7.36 - 7.78 ml, a donor compartment of 3.0 ml and a diffusion area of 1.77 cm². Phosphate buffered saline (PBS) at pH 7.4, with addition of 2% w/v Volpo N20 (oleyl ether of polyoxyethylene glycol), was used as a receptor solution, maintained at 35°C during the study, stirred at 600 RPM. Following 2 hours pre-incubation of the skin samples with the receptor solution, about 10 mg (5.6 mg/cm²) or 54 mg (30.5 mg/cm²) of the formulation were applied with a plastic rod and gently spread over the skin diffusion surface.

For the patch, a circular piece (16 mm) was punched out from the adhesive system and applied on the skin diffusion surface. Diffusion of the drug was allowed in non-occluded conditions for the gel and in occluded conditions for the patch. Receptor solution samples (1.2 ml) were automatically removed at 8-12-16-20-24 hours (after 0.8 ml receptor compartment priming). The samples were collected in 2 ml HPLC amber glass vials pre-sealed with septum crimp-caps containing 10 µl of a solution of trifluoroacetic acid (TFA) 10% and transferred into Eppendorf microtubes, and centrifuged at 14500 RPM during 10 min. Each supernatant (0.9 ml) was transferred in a 2mL HPLC amber glass vial. Analysis of the samples was performed by HPLC.

Results and conclusions:

By increasing 5-fold the loading (from 10.5 to 54.1 mg), the daily absorbed dose was increased by 3.4-fold (14.1 vs. 48.6 µg/cm²) and the maximum flux was 3.9-fold higher after 24 hours. Compared to the commercial patch, the daily absorbed dose was 5.3-fold lower for the 10 mg-loading (14.1 µg/cm² vs. 75.6 µg/cm²) but the drug loading is

5.1-fold lower (0.32 mg vs. 1.63 mg). Independent of the delivery system, (patch vs. gel), in vitro there was a nearly linear relationship between drug loading and drug absorption. Assuming, in addition, a linear relationship between application area and drug absorption, extrapolation of in vitro to in vivo data predicted a gel amount sufficient to deliver in vivo the targeted Oxytrol oxybutynin dose of 3900 µg per day to be 1.2 g of 3 % gel.

Cytotoxicity Study for Protocol No. 686647. (GLP) Extractables from the

[REDACTED] ^{(b) (4)} container components were evaluated in a study conducted according to the Good Laboratory Practice Regulations for Nonclinical Laboratory Studies, 21 CFR Part 58. Cultures of L929 mouse connective tissue cells were grown to a confluent monolayer in culture dishes. The growth medium was aspirated and replaced with fresh medium. An extract of the test and control specimens was placed on the cell layer and incubated at 37°C in an atmosphere of 4 to 6 % carbon dioxide for 24 hours. After incubation, the cells were inspected microscopically for cytotoxicity. No cytotoxicity was observed for any of the four container components of Oxybutynin gel 3% under the conditions of this study. Positive controls, negative controls, and media controls responded as expected.

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/s/

LAURIE L MCLEOD FLYNN
09/22/2011

LYNNDA L REID
09/22/2011
Concur

NDA Number:

202513

Applicant:

Antares Pharma, Inc.

Stamp Date:

8 February 2011

Drug Name:

oxybutynin gel 3%

NDA Type:

505 (b)(2)

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	X		Sponsor has referenced the previous finding of safety based on the nonclinical information submitted to support Ditropan.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Clinical PK data will be used to bridge this product with the reference product.
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		X	No GLP studies were requested or submitted for this NDA.
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?		X	No nonclinical studies were requested.

9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	X		
11	Has the sponsor addressed any abuse potential issues in the submission?		X	Oxybutynin is not known to have any abuse potential.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	NA		
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

No Pharmacology or Toxicology studies were requested for this NDA. A permeability study in pig ear skin was submitted along with literature references for oxybutynin.

The sponsor has referenced the Agency’s previous finding of safety for Ditropan (NDA 17-577), an oral oxybutynin product. Clinical PK data and topical irritation studies will be used to bridge between the safety of the 3% gel and Ditropan. Labeling for nonclinical sections will be based on the Ditropan label, which the sponsor has agreed to submit.

Ditropan label:

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae and Salmonella typhimurium test systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy

Category B

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN administered to women who are or who may become pregnant has not been established. Therefore, DITROPAN should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Excipients of Antares Oxybutynin Gel 3%:

No novel dermal excipients were used in the formulation of Antares Oxybutynin Gel 3%, as listed below:

Table 3.2.P.1-2 Concentration of components in Anturool oxybutynin gel, 3.0%, and maximum levels listed in Inactive Ingredients Guide

Ingredient	Oxybutynin Gel Concentration (% w/w)	Oxybutynin Gel Concentration (mg/g)	Maximum value from IIG for topical or transdermal
Oxybutynin	3.00	30.0	N/A
Diethylene glycol monoethyl ether, NF (DGME) ¹	(b) (4)	(b) (4)	25.00%
(b) (4)			84.95%
Hydroxypropyl cellulose, NF			4.0%
Propylene glycol, USP			98.09%
Butylated hydroxytoluene, NF			2.00%
HCl 0.1 M			4.00%
Purified water, USP			N/A

(b) (4)

Table 3.2.P.1-1 Description and Composition of the Anturool oxybutynin 3.0% Drug Product

Component and Grade	Regulatory/Safety Status	Function
Oxybutynin base	US DMF	Active Ingredient (b) (4)
Diethylene glycol monoethyl ether, NF (DGME)	USP/NF	
(b) (4)	USP/NF	
Hydroxypropyl cellulose (b) (4) NF	USP/NF	
Propylene glycol, USP	USP/NF	
Butylated hydroxytoluene, NF	USP/NF	
HCl 0.1 M	USP/NF	
Purified water, USP	USP/NF	

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/s/

LAURIE L MCLEOD FLYNN
04/20/2011

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